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10/542,839	12/13/2005	Tetsuo Kojima	14875-148US1 C1-A0231P-US	8994

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EXAMINER	
BRISTOL, LYNN ANNE	
ART UNIT	**PAPER NUMBER**
1643	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/542,839	KOJIMA, TETSUO	
	Examiner	Art Unit	
	Lynn Bristol	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *8-12 and 16-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 13-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 July 2007* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/16/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-18 are all the pending claims for this application.

2. Claims 1-3, 5, 13 and 15 were amended in the Response of 7/12/07.

3. Claims 8-12 and 16-18 are withdrawn from examination.

4. Claims 1-7 and 13-15 are all the pending claims under examination.

5. Applicants arguments and amendments to the claims have not overcome all of the outstanding rejections of record and the replacement drawings raise new grounds for objection.

Information Disclosure Statement

6. The non-patent literature reference cited in the IDS 5/16/07 has been considered and entered.

7. Applicants allege in the "Request for Initialed PTO Form 1449" of 4/27/07 that an IDS for the instant application was filed on 9/13/05, however, upon careful review of the file history, no such IDS entry appears in the record. Applicants are invited to access the file history through the public PAIR system to verify any such filing. The 1449 form filed on 4/27/07 has been placed in the file. Should Applicants wish to have the 1449 form initialed, they are invited (and required under 37 CFR 1.98(a)(2) for proper consideration and entry) to furnish a copy for each of the cited references in their response to this Office Action.

Withdrawal of Objections

Oath/Declaration

8. The objection to the oath/declaration for non-initialed and/or non-dated alterations is withdrawn. The copy of the original oath/declaration filed with the Response of 7/12/07 has been considered. Applicants' comments in the middle of p. 9 of the Response are acknowledged.

Specification

9. The objections to the specification for informalities are withdrawn for the following reasons:

a) The submission of the copy of original p. 1 from the specification does not contain non-initialed markings and obviates the objection.

b) The amendments to the specification to insert the section entitled "Brief Description of the Drawings" between the sections for the "Background of the Invention" and the "Detailed Description of the Invention" obviates the objection.

c) The amendments to the legends for Figures 1 and 2 to identify and explain each abbreviation (both Figures 1 and 2) and the steps involved in the process (Figure 2) obviate this objection.

Applicants' comments on the bottom of p. 9 to p. 10 of the Response are acknowledged.

Withdrawal of Rejections

Claims - 35 USC § 112, second paragraph

10. The rejection of Claims 1-7 and 13-15 for the recitation "screening for commonly shared light chains" is withdrawn in view of the deleted text from the claims.

Applicants' comments in the middle of p. 10 of the Response are acknowledged.

11. The rejection of Claims 3 and 13 in lacking antecedency for the recitation " the antibody heavy chain is Fd" is withdrawn in view of the amended claims to recite "the heavy chains of steps (a) and (d) are both Fd".

Applicants' comments in the middle of p. 10 of the Response are acknowledged.

Claims - 35 USC § 103

12. The rejection of Claims 1, 2, 4-7, 14 and 15 under 35 U.S.C. 103(a) as being unpatentable over Carter (J. Immunol. Methods 248:7-15 (2001); cited in the IDS of 4/14/06) in view of Winter et al. (US2004/0219643; published 11/4/04; priority filing date 6/28/02; cited in the 892 form of 12/7/06) is withdrawn.

On pp. 12-14, Applicants allege "Carter at page 10, Col. 2, lines 10-14, teaches pretty much the opposite approach, saying that one should start with "phage libraries that have vast H chain repertoires and a unique [] or very few [] different L chains" and "Carter does not teach introducing an antibody light chain library into a host that secretes a particular heavy chain as required by steps (b) and (d) of Claim 1.

On pp. 14-15, Applicants allege "According to Carter's method, one then screens that library to find an H/L combination that can bind to one of the desired antigens and a second H/L combination that can bind the other antigen, sequences the light chain of each combination to see if they are identical, and if they are, combine them into a bispecific antibody containing the two different heavy chains and two copies of the identical light chain. Nothing in Carter motivates one of skill in the art to take the opposite approach required by the present claims."

13. The rejection of Claims 1-3 and 13 under 35 U.S.C. 103(a) as being unpatentable over Carter and Winter as applied to claims 1 and 2, and further in view of Goldstein et al. (J. Immunol. 158:872-879 (1997)) is withdrawn.

See the reasons set forth above for the withdrawal of the Carter reference.

New Grounds for Objection

Drawings

14. The Replacement Sheets containing the corrected drawing figure(s) for Figures 1 and 2 are noted, however, Applicant is required to submit a marked-up copy of each Replacement Sheet including annotations indicating the changes made to the previous version. The marked-up copy must be clearly labeled as "Annotated Sheets" and must be presented in the amendment or remarks section that explains the change(s) to the drawings. See 37 CFR 1.121(d)(1). Failure to timely submit the proposed drawing and marked-up copy will result in the abandonment of the application.

Applicants' comments on the top of p. 10 of the Response are acknowledged, but do not satisfy the corrected drawing requirements.

New Grounds for Rejection

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

15. Claims 1, 2, 4-7, 14 and 15 are rejected under 35 U.S.C. 102(e) as being anticipated by Winter et al. (US2004/0219643; published 11/4/04; priority filing date 6/28/02; cited in the 892 form of 12/7/06).

The interpretation of Claims 1, 2, 4-7, 14 and 15 is of record as set forth in the Office Action of 2/16/07. Claim 2 is drawn to a method where the heavy chains have different amino acid sequences. The heavy chains would be inherently different in their sequences for the method of Claim 1 as well because the claim requires that the heavy chains recognize different antigens and one of skill in the art would expect the antibodies to vary in their sequence structure absent a showing to the contrary.

The method inventions for screening bi-specific antibodies produced from the same light chain (or VL) library are anticipated by Winter.

Winter at [0022] teaches that a plurality of dual specific ligands (VH/VL) can be combined to form a multimer $(VH/VL)_n$. For example, two different dual specific ligands are combined to create a tetra-specific molecule. Dual specific ligands may be combined into non-immunoglobulin multi-ligand structures to form multivalent complexes. In this case, the VH from each VH/VL pair would recognize a different antigen from the other, and the light and heavy variable regions may be on the same polypeptide chain, or alternatively, on different polypeptide chains [0023].

Winter also discloses antibodies produced by phage antibody library methods where all the antibodies share or have in common the same VL domain or light chain for anti-beta galactosidase (see Examples). Hence a multimer of Winter could comprise a molecule having the same two or shared VL domains paired with two VH domains against different antigens, and which would read on the intended antibody produced by the instant method.

Winter teaches method steps for producing the antibodies: a) selecting a first variable domain (VH1) by its ability to bind to a first epitope expressed from a phage display library, b) selecting a second variable region (VH2) by its ability to bind to a second epitope expressed from a phage display library, c) combining any one of the selected VH regions into a construct with a library of light chains or VL domains for expression by the same host; and d) selecting the dual-specific ligand or multimer by its ability to bind to the first and second epitopes recognized by the VH domains (or the ability of the light chains to bind to an antigen). The technology of Winter allows one of ordinary skill in the art to create and screen various kinds of libraries that are

encompassed by the instant claimed method. One of ordinary skill in the art could produce any host cell line secreting a selected heavy chain, introducing a light chain or VL library into the host cell, preparing a phage library presenting the antibodies constituted by the heavy and light chains or VH and VL domains, and a library which is selected that presents the antibodies uniquely bonding with a desired antigen. Thus the methods of Winter read on the methods of the instant claims. Winter specifically discloses multimeric antibodies that could comprise dual specific heavy chains or VH domains while sharing the same light chain or VL domain (i.e., anti-beta galactosidase).

One skilled in the art following the methods of Winter could produce not only a bi-specific antibody having VH and VL domains which recognized separate and distinct antigens but multimers where the antibody shared the same VL domains but different VH domains, and which were produced from the same light chain (or VL) library.

Note- the instant claimed methods (Claims 1 and 2) are not limited to and thereby required to produce a BsAb where the light chain is *commonly shared* by the different heavy chains. The specification teaches on p. 3, lines 24-26 "The present invention provides methods for screening for high-affinity light chains which correspond to arbitrary and different heavy chains, and which are commonly shared by the heavy chains." The scheme is outlined on p. 3, line 27- p. 4, line 6 (Figure 2). Thus light chains (or VL) directed to different antigens as taught by Winter than those to which the first and second heavy chains are directed fall within the scope of the instant claims.

Claims - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

16. Claims 1-3 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Winter as applied to claims 1 and 2 above, and further in view of Goldstein et al. (J. Immunol. 158:872-879 (1997); cited in the PTO 892 form of 2/16/07).

The interpretation of Claims 1-3 and 13 is of record as set forth in the in the Office Action of 2/16/07. Notably the limitation that the antibody comprising the heavy and light chains is Fab (Claims 3 and 13) has been deleted in the Response of 7/12/07, and therefore Goldstein would no longer apply.

The method inventions for screening bi-specific antibodies produced from the same light chain (or VL) library, was prima facie obvious at the time of the invention over Winter and Goldstein.

The interpretation of Winter is discussed supra. Winter appreciates forming heavy chains from antibody fragments but does not specifically disclose a Fd, and Goldstein specifically rectifies this deficiency.

Goldstein is cited for showing the utility of Fd fragments in generating recombinant antibodies.

One skilled in the art would have been motivated to have produced a method for screening commonly shared light chains in a bispecific antibody where the heavy chain was a Fd on the basis of the combined disclosure of Winter and Goldstein. Winter provides the motivation for making improved bispecific antibodies and methods for producing these molecules, and given the desirability of using smaller sized fragments that retain the full binding characteristics of the parent antibody, one skilled in the art would have been motivated to have used an Fd fragment as taught by Goldstein, because Goldstein teaches fusion methods, assembly of the Fd fragment with the light chain, and antigen specificity for the fragment upon assembly. One skilled in the art would have been reasonably assured of success in producing a screening method based on these disclosures because the technology was available to perform the steps to produce each of the different molecules on a step-wide basis according to the instant claimed method, and because bispecific antibodies sharing a common light chain were already known in the art based on the disclosure of Winter and that Fd fragments could be used in bispecific fusion proteins which resulted in successful assembly of the antibody into a functional, antigen-binding fragment based on Goldstein. Further because Winter discloses generating antibodies derived from different fragments, it

would have been apparent at the time of the invention based on the discussion of Winter supra, that one of ordinary skill in the art could have readily modified the antibody construction methods to use Fd fragments to obtain bispecific antibodies generated from heavy chains comprising Fd. Because Winter's results are unexpected and the antibodies are shown to work, one skilled in the art would have been reasonably assured of success in practicing any method steps of Winters that read on the instant method claim scope.

Conclusion

17. No claims are allowed.

18. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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